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Published in:
Supportive Care in Cancer

DOI:
10.1007/s00520-015-2909-0

Publication date:
2016

Support Care Cancer (2016) 24:1349–1355
DOI 10.1007/s00520-015-2909-0

ORIGINAL ARTICLE

Fatigue and its associated psychosocial factors in cancer patients on active palliative treatment measured over time

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Received: 8 April 2015 / Accepted: 16 August 2015 / Published online: 3 September 2015

Abstract
Purpose Fatigue is a frequently reported symptom by patients with advanced cancer, but hardly any prospective information is available about fatigue while on treatment in the palliative setting. In a previous cross-sectional study, we found several factors contributing to fatigue in these patients. In this study, we investigated the course of fatigue over time and if psychosocial factors were associated with fatigue over time.
Methods Patients on cancer treatment for incurable solid tumors were observed over 6 months. Patients filled in the Checklist Individual Strength monthly to measure the course of fatigue. Baseline questionnaires were used to measure disease acceptance, anxiety, depressive mood, fatigue catastrophizing, sleeping problems, discrepancies in social support, and self-reported physical activity for their relation with fatigue over time.
Results At baseline 137 patients and after 6 months 89 patients participated. The mean duration of participation was 4.9 months. At most time points, fatigue scores were significantly higher in the group dropouts in comparison with the group participating 6 months (completers). Overall fatigue levels remained stable over time for the majority of participants. In the completers, 42 % never experienced severe fatigue, 29 % persisted being severely fatigued, and others had either an increasing or decreasing level. Of the investigated factors, low reported physical activity and non-acceptance of cancer were associated significantly to fatigue.
Conclusion A substantial number of participants never experienced severe fatigue and fatigue levels remained stable over time. For those who do experience severe fatigue, non-acceptance of having incurable cancer and low self-reported physical activity may be fatigue-perpetuating factors.

Keywords Advanced cancer · Fatigue · Quality of life · Palliative phase · Cancer treatment

Introduction

The main aim of cancer treatment in patients with advanced incurable cancer is prolonging patients' life while ideally maintaining patients' quality of life. Patients with advanced cancer described fatigue to be their most distressing symptom limiting their quality of life [8, 28]. Although the knowledge of prevalence of fatigue, its course, and related factors in cancer survivors is extensive [1, 10, 17], the literature in patients with advanced cancer is scarce and prospective research in patients on active palliative cancer treatment is even more limited.

With the new treatment options nowadays, the palliative phase for patients with advanced cancer can last for years [20, 27] and has been compared with a chronic illness [40]. When we are able to prolong patients' life for years in the palliative phase, attention towards the occurrence of fatigue in this disease trajectory is relevant. In patients with advanced cancer, prevalence rates of fatigue of 33–90 % have been reported [7, 36, 38, 41]. Some researchers have suggested that fatigue will increase when a patient moves further in his palliative trajectory, in particular when being on active treatment

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[5, 7, 34]. Regrettably, most studies in patients within the palliative trajectory have studied pooled data of patients at different phases of their disease trajectory up to the final terminal phase [5, 7, 34]. Also, the majority of studies that report on fatigue in patients receiving palliative chemotherapy had not been designed to investigate fatigue as a primary research question. Some studies investigated fatigue in patients with advanced cancer when admitted to a palliative care unit or hospital for serious health deterioration [12, 18, 29, 36, 37]. These patients were mostly at a late palliative stage or terminal phase and did not receive anticancer treatment. In an observational study aimed at fatigue during anticancer therapy in 99 patients with different stages of disease, fatigue levels remained stable over 2 months [6]. We reported in a cross-sectional study severe fatigue in 47 % palliative patients on anticancer treatment, with higher fatigue scores in patients who were receiving further lines of treatment [31]. A longitudinal study is needed to determine whether fatigue increases during palliative cancer treatment.

In cancer survivors, a model was developed to explain persistent severe fatigue obviously not associated to somatic factors [35], and in addition, a successful therapy based on this model was developed [15, 16]. In the abovementioned cross-sectional study in patients with advanced cancer, we found several non-somatic factors associated to fatigue similar to those in cancer survivors [32]. The psychosocial factors such as non-acceptance of having incurable cancer, anxiety, depressive mood, fatigue catastrophizing cognitions towards fatigue, sleeping problems, discrepancy in (expected and experienced) social support, and low perceived physical activity were all associated to fatigue. In the current longitudinal study, we wanted to investigate these factors prospectively for their contribution to fatigue over time in patients with incurable cancer, while on treatment. Our hypothesis was that the same psychosocial factors are associated with fatigue over time and contribute to fatigue over time independently.

Exploring the factors related to the course of fatigue prospectively might bring us a step forward to the development of a treatment model, on which interventions for fatigue can be developed also in the palliative phase of cancer treatment.

Patients and methods

Between December 2008 and June 2010, patients on or about to start with treatment for advanced, incurable cancer from the departments of medical oncology of a university and a regional hospital in the southeastern part of the Netherlands were asked to participate in this study. Physicians preselected potentially eligible patients based on the following inclusion criteria: diagnosis of advanced, incurable cancer; able to receive palliative (symptom reducing and/or life prolonging) cancer treatment; and able to fill in and return questionnaires in Dutch. The main investigator (MP) approached potential participants by telephone. She informed them about the study and additional written information was sent to those who were interested in the study.

Participants from the university medical center had the opportunity to either complete the baseline questionnaires using a computer at the outpatient clinic (in combination with a regular visit to the clinic) or fill in a paper-and-pencil version at home. Patients from the regional hospital all received the paper-and-pencil version at home. After the baseline investigation, the fatigue questionnaire Checklist Individual Strength was sent every month for 6 months. Six months after inclusion, a final set of follow-up questionnaires was sent. A maximum of two telephone calls were made by the investigator to complete the baseline and follow-up data. For the monthly sent out fatigue questionnaires, no additional attempts were made to complete these. Permission to conduct the study was obtained from both institutional review boards of the participating hospitals, although this study did not fall under the Medical Research Involving Human Subjects Act. All participants provided verbal consent.

Instruments

General information on demographical characteristics, stage and type of cancer, and current treatment was obtained from a general questionnaire, eventually supplemented with data from medical records. Fatigue severity was assessed with the subscale fatigue of the Checklist Individual Strength (CIS). This subscale consists of eight items asking for fatigue severity over the last 2 weeks; each item is scored on a 7-point Likert scale; range is from 8 to 56; higher scores indicate more severe fatigue. The validated cut-off score of 35 or higher was used to determine severe fatigue [42, 43]. This score of 35 is about two times the standard deviation (sd) above the mean score of healthy controls. The subscale physical activity, consisting of three items on a 7-point Likert scale, was used to measure self-reported physical activity. Higher scores are indicative for lower self-reported physical activity [3, 9]. The CIS is a well-validated instrument with excellent psychometric properties [3, 9, 43].

Inappropriate coping with disease was measured with the subscale Acceptance of the Illness Cognition Questionnaire (ICQ) for chronic diseases. This subscale measures the degree of acceptance of having cancer and consists of six items on a 4-point scale from 1 (do not agree) to 4 (completely agree) [14]. It has shown good reliability with Cronbach's alpha coefficients ranging from 0.84 to 0.91 in patients with chronic diseases [13].

Anxiety was measured with the subscale anxiety of the Hospital Anxiety and Depression Scale (HADS) [19, 24,

45]. To assess depressive mood, the subscale depression of the HADS was used [19, 24]. Both subscales consist of seven items on a 4-point Likert scale. The HADS is an extensively used and validated instrument [44].

Fatigue catastrophizing was measured by the Fatigue Catastrophizing Scale (FCS), consisting of 10 items on a 5-point scale from 1 (never true) to 5 (all of the time true) [4, 21]. Higher scores are indicative for more fatigue catastrophizing. A total score is derived by computing the mean of 10 ratings. This subscale has a good reliability with a Cronbach's alpha of 0.85 [21].

Sleeping problems were measured by the sleep subscale of the Symptom Checklist (SCL-90) [2], consisting of three items on a 5-point scale from 1 (not at all) to 5 (very much). Higher scores indicate lower quality of sleep. Patients were asked if they, during the last month, (a) slept well, (b) had difficulty with falling asleep, and (c) woke up early in the morning. This subscale has a good reliability with a Cronbach's alpha of 0.73 [2].

Discrepancy between the received and desired amount of social support was measured by the van Sonderen Social Support List-Discrepancies (SSL-D) [33], consisting of eight items on a 4-point scale. Scores for the SSL-D range from 8 to 32. Higher scores are indicative for a higher discrepancy. This instrument has a good reliability with a Cronbach's alpha of 0.95 [11].

Statistical methods

Descriptive statistics and frequencies were generated to determine the sample characteristics and the course of fatigue. To give insight into the course of fatigue, we also differentiated between a group who dropped out (group DO) and a group that still participated at 6 months (completers). The non-parametric Mann-Whitney test was used to investigate differences in fatigue scores between the groups DO and completers. A linear regression analysis (enter method) was performed to assess the relationship

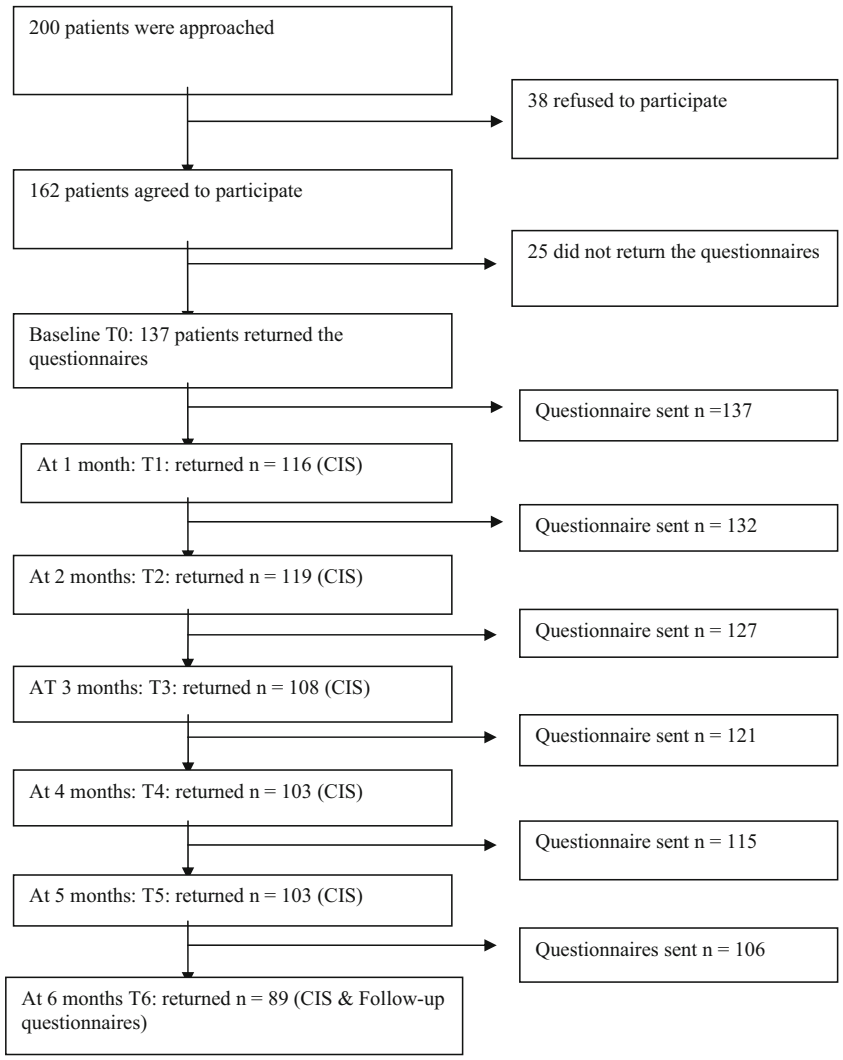

Fig. 1 Flowchart of the number of participants at the different time points

Table 1 Baseline demographic and cancer- and treatment-related characteristics

Characteristics	Participants, *n* (%)
Participants	137
Female gender	84 (61)
Male gender	53 (39)
Mean age, years (range)	59 (30–79)
Marital status	
Married	111 (81)
Single (unmarried, divorced, widowed)	26 (19)
Type of cancer	
Breast	41 (30)
Gastrointestinal	41 (30)
Urogenital	5 (11)
Gynecological	13 (9.5)
Bone & soft tissue	13 (9.5)
Other	14 (10)
Treatment modalities	
Chemotherapy	72 (53)
Oral-targeted therapy	21 (15)
Hormonal therapy	20 (15)
Chemo-targeted therapy	19 (14)
Radiotherapy	2 (1)
Chemoradiotherapy	1 (1)
No actual treatment[a]	2 (1)
Treatment line	
First-line	92 (67)
Second-line	28 (20)
Third-line	12 (9)
Fourth-line	5 (4)

[a] Two patients were about to start with their first-line treatment

of psychosocial factors at baseline to fatigue over time. SPSS software (version 20) was used to analyze our data (SPSS Inc., Chicago, IL, USA).

Results

Two hundred patients with advanced cancer receiving treatment were approached for this study. One hundred and sixty-two patients agreed to participate and 137 of them (69 %) filled in the baseline questionnaires. Non-participants (n = 63) did not differ from the participants with regard to sex, age, and cancer diagnosis as has been reported elsewhere [31]. Figure 1 shows the number of participants at the different time points. The mean duration of follow-up for all participants (AP) in the study, including dropouts, was 4.9 months. During the study period of 6 months, 89 patients participated during all 6 months (completers), the remaining 48 patients were considered as the group DO and they participated for a mean period of 2.7 months (range 1–5 months). Twelve of them only filled in the baseline measurements. Reasons for dropout were as follows: no longer being able to fill in questionnaires (n = 7), died during the study (n = 20), and not wanting to participate anymore (n = 4). Seventeen patients gave no reason for dropout. Demographic and cancer- and treatment-related characteristics of all participants at baseline are shown in Table 1. We found no significant differences between the groups DO and completers on gender, age, type of cancer, treatment modalities, and treatment line (not shown).

The mean fatigue scores and percentages of severely fatigued patients at the different time points of AP, of the group DO, and the group completers are shown in Table 2. The mean fatigue scores in all three groups remained stable over time. At time points T1, T2, T3, and T4, the mean fatigue scores of the group DO were significantly higher in comparison with the completers. Also, the severely fatigued percentage remained quite stable over time within the group AP. The group DO showed an increase in percentages of severely fatigued patients during the first 2 months, and the completers showed the opposite. After the third month, the percentage of severely fatigued stabilized in both subgroups.

Table 2 Mean fatigue scores and percentages of severe fatigue during 6 months

	All participants N = 137		Group dropout N = 48		Completers N = 89		Differences in mean fatigue scores: group dropout and completers P value
	Mean fatigue (sd)	Severe fatigue, % (n/N)	Mean fatigue (sd)	Severe fatigue, % (n/N)	Mean fatigue (sd)	Severe fatigue, % (n/ N)	
Baseline/T0	32 (13.2)	47 (64/136)	35 (13.1)	54 (26/48)	31 (13.1)	43 (38/89)	0.187
T1	32 (12.9)	46 (53/116)	38 (11.7)	67 (20/30)	30 (12.8)	38 (33/86)	0.007
T2	32 (12.8)	40 (48/119)	38 (12.9)	59 (19/32)	29 (11.9)	33 (29/87)	0.001
T3	32 (13.8)	45 (49/108)	38 (14.2)	57 (12/21)	31 (13.4)	43 (37/84)	0.045
T4	31 (13.9)	44 (45/103)	39 (13.6)	58 (11/19)	30 (13.1)	41 (34/84)	0.017
T5	31 (13.8)	44 (45/103)	38 (13.0)	50 (7/14)	31 (13.4)	43 (38/89)	0.082
T6	32 (13.9)	44 (39/89)			32 (13.9)	44 (39/89)	

Table 3 Linear regression to predict fatigue severity over the 6-month follow-up

Independent variables at baseline	Beta	Dependent variable: mean CIS fatigue of all follow-up assessments		
		95 % CI for *B*		*P* value
		Lower bound	Upper bound	
Acceptance (n = 89)	−0.263	−1.366	−0.045	0.037
Catastrophizing (n = 87)	0.049	−0.322	0.474	0.704
Depressive mood (n = 86)	0.204	−0.169	1.635	0.110
Anxiety (n = 86)	−0.672	−0.998	0.495	0.504
Sleep quality (n = 79)	−0.009	−0.870	0.800	0.933
Discrepancies social support (n = 89)	−0.079	−1.702	0.739	0.434
Self-reported physical activity (n = 88)	0.504	0.580	1.406	0.000

R^2 = 0.514

In the completers, 42 % (37/89) never experienced severe fatigue and 29 % (26/89) experienced severe fatigue at all time points. Thirteen patients became severely fatigued (15 %) and in 12 patients (14 %) it decreased in the 6-month follow-up, from severely to not severely fatigued. The linear regression analysis within the completers showed that 51 % of the variance on fatigue severity may be explained by the psychosocial factors, of which the factors non-acceptance of having incurable cancer and self-reported physical activity contributed significantly to the severity of fatigue over the 6-month period (see Table 3).

Also the scores of the investigated psychosocial variables remained quite stable over time (see Table 4).

Discussion

In this study, we investigated the course of fatigue over a period of 6 months in patients with advanced cancer receiving palliative cancer treatment. Additionally, we prospectively explored which psychosocial factors contributed to the severity of fatigue over this period. To our knowledge, this is the first study in which the severity of fatigue is longitudinally observed in cancer patients on active treatment in the palliative phase.

Of the patients who were able to participate during the total period of 6 months, 42 % were not severely fatigued and did not become so during this period. About a quarter of these patients was severely fatigued and remained so. In 15 %, a decrease from severe fatigue to non-severe fatigue occurred, and in 12 % of patients, fatigue level increased from non-severe to severe fatigue. Interestingly, in two thirds of the patients, the fatigue level did not change during the course of the study and the mean score was rather stable for the whole group participants during the 6-month study period. However, patients who dropped out somewhere during the study often had a significantly higher fatigue level at the various time points compared to the patients who remained in the study.

Although fatigue is the most often reported symptom in patients with incurable cancer [5, 36, 37], we demonstrated for the first time that not every patient suffers from severe fatigue. In the group of patients who remained in the study, the percentage of severely fatigued patients was lower compared with patients who dropped out. This might suggest that the patients who still participated after 6 months are part of a relatively fit group. This suggestion is supported by the finding of higher fatigue scores at baseline in the group who

Table 4 Baseline and follow-up values of investigated psychosocial factors

Variables	Baseline			Follow-up		
	N	Median	Interquartile range	*N*	Median	Interquartile range
Acceptance	137	17	6	85	18	6
Catastrophizing	133	16	7	86	18	9
Depressive mood	134	4	4	87	4	5
Anxiety	134	5	6	87	4	7
Sleep quality	124	6	4	78	5	4
Discrepancies social support	136	8	1	84	8	1
Self-reported physical activity	137	12	9	82	11	11

dropped out and by the finding that the main reason for dropout was deterioration of the health status or death. Moreover, the percentage of patients that changed levels of fatigue severity in the group that continued follow-up was rather low (29 %), suggesting that several factors perpetuate the fatigue during this observation period of 6 months. A study that would include all patients at the same time within their disease trajectory, i.e., at primary diagnosis of incurable cancer, and that will follow the patients longitudinally from that time onwards might provide more insight into the course of fatigue and associated symptoms.

Two of the investigated fatigue-associating factors were related to the course of fatigue (the mean fatigue score during the follow-up period), namely, a low level of self-reported physical activity and difficulties in acceptance of having incurable cancer. This implicates that influencing and addressing these factors might reduce fatigue and may have an improvement on the quality of life in these patients. Few studies already addressed the issue of physical activity and focused on exercise training to tackle fatigue but did not reach clinically relevant reductions in fatigue [30]. Other studies had small samples and mainly investigated the feasibility of exercise programs in patients in the palliative phase [22, 25, 26]. It is important to remark that in our study, we did not measure actual physical activity, for example by actimetry, but assessed the self-reported level of physical activity.

To reflect on the difficulties of acceptance of having incurable cancer relating to fatigue, we only found in literature that acceptance of having incurable cancer can be a specific factor for palliative patients. It has been described as a psychological process that evolves throughout the course of a disease trajectory [39]. To our awareness, however, this is the first study that found a relation with problems of acceptance with having incurable cancer and fatigue.

For five other postulated perpetuating factors, we could not show a relation with the course of fatigue in the palliative phase. There might be two reasons why we did not find such a relation. First, it could be explained by individual differences in relevance of these factors, an observation which has also been made in fatigue in cancer survivors [15, 32]. Second, it could be that we investigated the wrong factors. This would mean that factors other than postulated in our study may contribute to the course of fatigue. It is, however, difficult to state which factors we could have missed because literature on this topic is very scarce.

There are several limitations to be acknowledged. Although all participants had advanced cancer at baseline, the patients were not at the same point in their disease trajectory. At baseline, two patients were just about to start with their first-line treatment, while all other participants were somewhere within their disease trajectory varying from the first to the fourth treatment line. Regrettably, we have no information whether patients still received treatment at 6 months follow-up and if so, the kind of treatment or treatment line they were receiving at the final assessment, nor the effect on oncologic parameters. In line with this, we have no information on the median survival time of the participants.

Another limitation might be the questionnaires we used. We used the subscale anxiety of the HADS as a proxy for heightened fear of disease progression. We wanted to get more insight into fear related to having an incurable disease. At the time of study, such a validated questionnaire was not available in Dutch. Recently, such a questionnaire, the "fear of progression questionnaire," has been validated and this one could have been more suitable [23].

To summarize, an important conclusion from this study is that not all patients who continue active treatment within the palliative trajectory suffer from severe fatigue and only a minority change fatigue level over time. For those who do experience severe fatigue, non-acceptance of having incurable cancer and low perceived physical activity seem to be fatigue-perpetuating factors. Fatigue interventions might therefore be directed at helping palliative patients to accept the cancer and improving their level of (subjective) physical activity.

Acknowledgments We would like to thank Tineke Smilde and Bernadine van de Walle – van de Geijn for approaching patients and coordinating the recruitment of potential participants at the Jeroen Bosch Hospital. Also, we would like to thank Lianne Vermeeren and Carel Kruip of the Expert Center Chronic Fatigue for entering all the data.

Funding Financial support was obtained from the Paul Speth Foundation.

Conflict of interest The authors declare that they have no competing interests.

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